a cell using the compounds, and compositions that contain the delivery-enhancing compounds, are also provided, as are methods for treating bladder cancer. Included among the therapeutic and diagnostic agents that can be delivered are proteins and nucleic acids, including gene therapy vectors.

Status of the Application

Claims 1-61 are pending with entry of this amendment. Claims 1-55 were originally filed, and entry of claims 56-61 was requested in Applicants' previous amendment. Claims 56-61 are presently indicated as being withdrawn from consideration as being directed to a nonelected invention.

Claims 1-55 remain rejected under 35 USC § 112, first paragraph. Claims 1, 7, 12, 16, 23, 29, 41-42, 45, 54 and 55 stand rejected under 35 USC § 102(b). Claims 1-6, 8, 12-15, 17, 23-26, 30 and 39-55 stand rejected under 35 USC § 103(a), and claims 1, 8-10, 12, 17-19, 23 and 30-32 stand rejected under 35 USC § 103(a) on a different ground. Claims 1, 8-9, 11-12, 17-18, 20, 23, 30-31, 33 and 37 remain rejected under 35 USC § 103(a) on a third ground.

Claims 21-22 and 35-36 are indicated as being free of the art.

The Withdrawal of Claims 56-61

In their amendment mailed March 29, 1999, Applicants requested entry of new claims 56-61. These claims are directed to methods of administering diagnostic agents using a reagent having Formula I, while the previously pending claims were directed to methods of administering therapeutic agents using a reagent having Formula I.

New claims 56-61 were withdrawn from consideration by the instant Office Action as allegedly being drawn to a nonelected invention. The Office Action cites MPEP § 821.03 in support of this refusal to consider the new claims. However, the Office Action has ignored a critical portion of § 821.03, that which requires the Examiner to establish that the new claims are directed to "an invention that is independent or distinct from the invention originally claimed" and to present reasons for this determination. Here, the Office Action has not even made an assertion that the new claims cover an independent or distinct invention, let alone

provided reasons for this determination. Therefore, the withdrawal from consideration of claims 56-61 is improper.

Priority Date

According to the Office Action, the instant application is not entitled to claim priority to the January 8, 1996 filing date of Ser. No. 08/584,077 (now US Patent No. 5,789,244) because the parent application does not disclose the compounds of Formulas I-V that are encompassed by the claims of the instant application.

Applicants note that none of the cited references are dated between the claimed priority date and the actual filing date of the instant application. Moreover, Applicants need not depend upon the claimed January 8, 1996 priority date to overcome the rejections, as discussed below. Accordingly, Applicants need not address the priority claim at this time.

The 35 U.S.C. § 112, First Paragraph Rejection

Claims 1-55 remain rejected under 35 USC § 112, first paragraph, because the claims allegedly include subject matter that is not described in the specification in such a way as to enable one of skill in the art to make and/or use the invention.

A first basis of the rejection is essentially that the specification is not enabling because it is not clear which impurities of BigCHAP enhance delivery of therapeutic agents. The Office Action points out that, according to Applicants' specification, impurity I does not increase gene expression (page 30, line 14). Impurities II and II, on the other hand, do demonstrate improved gene transfer and expression, as the Office Action correctly points out. The Office Action asserts that because the formulas for impurities I, II and III are not provided in the specification, it is unclear which of the claimed formulas enhance delivery of DNA.

Applicants respectfully traverse this rejection. Applicants' independent claims 1, 12, 23, 41 and 54 specifically set forth the generic formula of compounds that enhance DNA delivery. Numerous dependent claims specify particular species within these genera that exhibit the delivery enhancing activity. The only evidence set forth in the Office Action in support of the assertion that compounds within this generic formula do not necessarily exhibit delivery enhancing activity is that BigCHAP impurity I does not increase gene expression. However,

impurity I is not within the scope of the generic formula set forth in Applicants' claims. This is evidenced by Figure 22 of US Ser. No. 09/112,074, which is a continuation-in-part of the instant application. A copy of this Figure is enclosed herewith. The failure of impurity I to enhance gene expression is thus not relevant to whether Applicants' specification provides sufficient teaching as to which compounds within the scope of the generic formulas exhibit delivery enhancing activity. No evidence is of record to support the Office Action's position that the specification does not provide sufficient teaching as to which compounds exhibit gene delivery-enhancing activity. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971).

With respect to whether the instant specification demonstrates enhanced delivery of a therapeutic gene using the claimed invention, Applicants' previous response pointed out that, as stated in Example 6 (page 25), the administering an RB-expressing adenoviral vector resulted in "enhanced expression using an ethanol or ["or" was mis-typed as "of" in previous response] Big CHAP (CALBIOCHEM®) formulation," for which results "are shown in Figure 9." The instant Office Action asserts that Figure 9 appears to demonstrate expression using ethanol alone as an enhancing agent and not BigCHAP. However, Applicants respectfully point out that the right-hand panel of Figure 9 (lanes 7 and 8) does show enhanced delivery using Big CHAP. Applicants note with appreciation the Examiner's indication that the arguments based on Example 8 and the several examples demonstrating expression of a marker gene were found to be persuasive.

The Examiner found persuasive Applicants' argument that some of the references cited in the previous Office Action as demonstrating that the gene therapy art was unpredictable at the time Applicants' invention was made do point out that gene therapy could be improved by methods of enhancing delivery of DNA. Applicants have demonstrated that the claimed formulations do enhance DNA delivery (see above and Applicants' previous Amendment). However, this argument is not found sufficient to overcome the rejection because, according to the Office Action, it is not clear which impurities in the instant application can be used to enhance delivery of DNA. As established above, however, the instant specification does set forth

a generic formula that encompass the compounds that have the DNA delivery-enhancing activity. This formula does not encompass Impurity I, which does not exhibit such delivery-enhancing activity. Therefore, no evidence exists that any compounds within the scope of the generic formula do not enhance gene delivery, so Applicants' specification must be presumed to be enabling.

The Office Action dismisses Applicants' assertion that the hundreds of gene therapy clinical trials that are now in progress are persuasive evidence that gene therapy inventions are not *per se* unpatentable. According to the Office Action, "while clinical trials may provide a possibility of success, based on what is known in the art at the time of filing, one of skill could not predict whether a therapeutic effect could be obtained with a reasonable expectation of success." This statement is directly contradicted by the MPEP ("[b]efore a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. . . . Thus, as a general rule, if an applicant has initiated clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility" (MPEP § 2107.02, emphasis in original)). This section of the MPEP is based upon case law of the Federal Circuit Court of Appeals and the Court of Customs and Patent Appeals (cited in MPEP § 2107.02), which case law also directly contradicts this statement. Accordingly, Applicants respectfully request that the Examiner provide Applicants with that controlling legal authority which allows the Office Action to ignore this long-standing body of law. In the absence of such legal authority, this ground of rejection is clearly improper and should be withdrawn.

Finally, Applicants disagree with the Office Action's statement that "the claims are all directed toward administering a therapeutic or pharmaceutical protein which has not been adequately disclosed in the specification such that one of skill would have a reasonable expectation of success in obtaining a therapeutic effect" (Office Action, page 6, first full paragraph). Not all of Applicants' claims require a therapeutic effect. For example, claims 41-55 are simply directed to compounds of Formula I. No limitation as to a particular use for the

compositions is found in these claims. In situations such as this where "a compound or composition claim is not limited by a recited use, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention. MPEP § 2164.01(c).

Applicants' specification provides experimental data which supports the assertion that the compounds encompassed by these composition claims are useful not only for enhancing delivery of DNA to cells *in vivo* to achieve a therapeutic effect, but also for delivering marker genes *in vivo*. Moreover, the specification states that such compounds are also useful for enhancing delivery of agents to cells *in vitro* (page 16, lines 24-26). It would be readily apparent to those familiar with the technological field of the invention that delivery of DNA to cells *in vitro* is useful for producing proteins, including therapeutic and other proteins, *in vitro*. It is well-settled that a well-established utility such as this need not be explicitly set forth in an application. MPEP § 2107.01(B). No therapeutic effect is needed to demonstrate enablement for such uses. Thus, because the application is unquestionably enabling for these uses, the application is enabled for the composition claims.

Claims 56-61, which are directed to delivery of diagnostic reagents, also do not require any evidence of a therapeutic effect to establish enablement. Therefore, this ground of rejection is not applicable to these claims.

Claims 7, 16 and 29 are directed to methods of administering a protein, and compositions that contain proteins, in which the specified delivery enhancing agents are employed. According to the rejection, the specification does not demonstrate that one of skill in the art would have a reasonable expectation of success in obtaining a therapeutic effect by administering a protein. However, the PTO has not met its initial burden of making a *prima facie* case of showing that a claimed invention is not enabled under 35 USC § 112, first paragraph (MPEP § 2164.04). This ground of rejection is not supported by any specific evidence or reasoning that the well-established use of proteins as therapeutic agents would somehow be defeated by administering the proteins in a composition that includes the compounds set forth in Applicants' claims. Accordingly, this rejection should be withdrawn.

The 35 U.S.C. § 102(b) Rejection

Claims 1, 7, 12, 16, 23, 29, 41-42, 45, 54 and 55 stand rejected under 35 USC § 102(b) as allegedly being anticipated by Aungst *et al.* (*Int. J. Pharm.* (1993) 53: 227-235). The cited reference discusses delivery of insulin in a formulation that includes Big CHAP. Although Big CHAP is not encompassed by the formulas set forth in Applicants' claims, the rejection asserts that the Big CHAP taught by Aungst *et al.* inherently contains the impurity of Formula I.

Applicants respectfully traverse. When relying on inherency for an anticipation rejection, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art." MPEP § 2112, quoting with approval *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(emphasis added). This is not true for Big CHAP, as not all preparations of Big CHAP include impurities that can enhance delivery of a therapeutic agent. This is well-stated by the Examiner in the Office Action mailed September 29, 1998: "Thus, it is not clear that pure BigCHAP, any commercial brand of BigCHAP with any impurities, or any lot or batch of BigCHAP from one particular company can be used in the method claimed such that delivery is **enhanced**" (page 3, first full paragraph, emphasis in original). The instant inventors found that the delivery-enhancing impurities were present in one particular lot of Calbiochem's BigCHAP. The Sigma BigCHAP did not have the impurities and did not enhance delivery of agents to cells. Thus, one cannot assume that any commercial preparation of BigCHAP, including that used by Aungst *et al.*, will necessarily result in enhanced delivery of DNA or other agents. Therefore this ground of rejection is improper and should be withdrawn.

The 35 U.S.C. § 103(a) Rejections

Claims 1-6, 8, 12-15, 17, 23-26, 30 and 39-40 remain rejected under 35 USC § 103(a) as allegedly being unpatentable over Aungst *et al.* (*Int. J. Pharm.* (1993) 53: 227-235) in view of Carson *et al.* (US Patent No. 5,804,566, issued September 8, 1998 and filed November 1, 1994). Applicants respectfully traverse this rejection.

A proper *prima facie* case of obviousness requires that all of the claim limitations must be taught or suggested by the prior art. MPEP § 2143.03, *citing In re Royko*, 180 USPQ 580 (CCPA 1974). Moreover, an obviousness rejection cannot be founded on inherency. *In re*

Rijckaert, 28 USPQ2d 1955 (Fed. Cir. 1993)("'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.' *In re Spormann*, 53 C.C.P.A. 1375, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966). Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. *See In re Newell*, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).").

Neither of the cited references provides any suggestion that one of ordinary skill in the art should use a compound within the scope of Applicants' claims to enhance delivery of an agent. Aungst *et al.* suggests, at most, that one should use BigCHAP. However, absolutely no suggestion is made that the delivery-enhancing activity is due to an impurity in BigCHAP. Nor is there any suggestion of compounds within the scope of the formulas set forth in Applicants' claims, most of which are not found in any preparations of BigCHAP. Only by referring to Applicants' disclosure can one find such teachings. It is black letter law that, for *prima facie* obviousness, both the suggestion and the reasonable expectation of success must be founded in the prior art, not in Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Therefore, *prima facie* obviousness is not established and the rejection should be withdrawn.

The rejection makes several unfounded assumptions regarding the compounds of dependent claims 42-53, assuming that these compounds are all obvious variants of the impurity found in BigCHAP as taught by Aungst *et al.* However, neither of the cited references provides any characterization of the structures of the delivery-enhancing agents from which the Office Action can conclude what is or is not an obvious variation.

Claims 1, 8-10, 12, 17-19, 23 and 30-32 remain rejected under 35 USC § 103(a) as allegedly being unpatentable over Aungst *et al.* in view of Carson *et al.*, and further in view of Wills *et al.* (1994) *Human Gene Ther.* 5: 1079-1088. This ground of rejection is improper for the same reason as the previous rejection. Again, Aungst *et al.* is relied upon for the teaching that impurities in BigCHAP can enhance delivery of agents. According to the rejection, "BigCHAP as taught by Aungst *et al.* obviously comprises Formula I as claimed" (Office Action, page 9). However, the rejection points to absolutely no teaching in the cited references that BigCHAP even contains any impurities or of any compounds within the scope of Formula I, let alone that

these impurities or compounds of Formula I have any delivery-enhancing activity. It is only by reference to Applicants' disclosure that one of ordinary skill in the art could determine that compounds encompassed by Formula I have such delivery-enhancing activity. Therefore, this ground of rejection is improper and should be withdrawn.

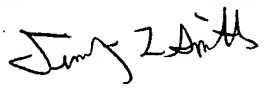
Claims 1, 8-9, 11-12, 17-18, 20, 23, 30-31, 33 and 37 remain rejected under 35 USC § 103(a) as being unpatentable over Aungst *et al.* in view of Carson *et al.*, and further in view of Takahashi *et al.* (*Proc. Nat'l. Acad. Sci. USA* (1991) 88: 5257-5261). As do the previous grounds of the obviousness rejection, this rejection relies upon the Aungst *et al.* paper to provide the suggestion to use a compound as set forth in Applicants' claims as a delivery-enhancing reagent. However, none of the cited references provide any suggestion that impurities in BigCHAP have delivery-enhancing activity, let alone that compounds of Formula I have such activity. It is only by reference to Applicants' disclosure that one can find this teaching. Therefore, this ground of rejection is improper.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned attorney at (415) 576-0200.

Respectfully submitted,



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